Re: Population-Based, Case–Control Study of HER2 Genetic Polymorphism and Breast Cancer Risk

Overexpression of the HER2 (also known as NEU and ERBB2) proto-oncogene is associated with poor prognosis among female patients with breast cancer. A single-nucleotide polymorphism in the transmembrane domain-coding region at codon 655 of the HER2 gene that exchanges an isoleucine (Ile) for a valine (Val) was associated with breast cancer in a Chinese study *(1),* particularly among subjects younger than 45 years of age, but subsequent evidence did not confirm this finding. In a recent study among Ashkenazim, Rutter et al. *(2)* also found an association, particularly in women with early-onset breast cancer and in women with a family history of breast cancer. We used the kin–cohort design *(3)* to evaluate the HER2 single-nucleotide polymorphism in a cohort of female relatives of case patients with breast cancer within a large cohort study.

In a cohort of 146 022 U.S. radiologic technologists, 83 748 women responded to at least one of two surveys (between 1984 and 1989 and between 1993 and 1998) *(4).* Of 1345 women, most of whom were white, who reported a medically confirmed primary breast cancer and were alive on December 31, 1999, 746 probands were located who returned a blood sample by mail and provided, by telephone interview, a family census of female first-degree relatives including their birth and death dates and their cancer history. Demographic, reproductive, and family cancer histories were similar among participants and nonparticipants, i.e., women who did not provide a blood sample. The participants provided data on 189 first-degree relatives with breast cancer and 2231 without breast cancer (Table 1). The probands were genotyped with a TaqMan 5′-nuclease assay (Integrated DNA Technologies, Coralville, IA) described elsewhere *(2).*

We used a marginal likelihood approach to estimate the absolute risk in a kin–cohort study *(3)*; the statistical analysis was based on the relatives' breast cancer experience and indirect information on their HER2 genotype derived from the known genotype of the corresponding proband. Cumulative risk ratios (RRs) were calculated up to age 50 years and 70 years for carriers of the Val allele compared with noncarriers. The variance of the RR was assessed by bootstrap sampling of families.

The frequency of the Val allele in case probands was 24%, in agreement with earlier reports in Caucasians *(5–7).* If we assume a dominant mode of inheritance, the cumulative RRs for Ile/Val and Val/Val genotypes versus Ile/Ile genotypes were 0.70 (95% confidence interval [CI] = 0.30 to 1.85) up to age 50 years and 1.51 (95% CI = 0.83 to 2.49) up to age 70 years. If we assume a recessive mode of inheritance, the RRs for the Val/Val genotype versus the Ile/Ile and Ile/Val genotypes were 1.37 (95% CI = 0.00 to 3.98) up to age 50

Table 1. Descriptive characteristics of case patients with breast cancer (probands) from the U.S. Radiologic Technologists Health Study and their female first-degree relatives with and without breast cancer and relative risk for breast cancer by HER2 genotype*

Characteristics at time of interview (1999–2001)	Case patients with breast cancer,† No. (%)	Female first-degree relatives		Relative risk (95% CI)	
		With breast cancer, No. (%)	Without breast cancer, No. (%)	Up to age 50 y	Up to age 70 y
Year of birth					
<1900	0 (0.0)	19 (10.1)	165 (7.4)	—	—
1900–1929	155 (20.8)	110 (58.2)	700 (31.4)	—	—
1930–1939	201 (26.9)	28 (14.8)	232 (10.4)	—	—
1940–1949	276 (37.0)	19 (10.1)	269 (12.1)	—	—
1950–1959	114 (15.3)	10 (5.3)	303 (13.6)	—	—
⩾1960	0 (0.0)	3 (1.6)	562 (25.2)	—	—
Age at diagnosis					
<40 y	114 (15.3)	21 (11.1)	—	—	—
40–49 y	297 (39.8)	28 (14.8)	—	—	—
50–59 y	203 (27.2)	42 (22.2)	—	—	—
60–69 y	90 (12.1)	49 (25.9)	—	—	—
⩾70 y	42 (5.6)	49 (25.9)	—	—	—
Relationship to the proband					
Mother	—	98 (51.9)	646 (29.0)	—	—
Sister	—	84 (44.4)	877 (39.3)	—	—
Daughter	—	7 (3.7)	708 (31.7)	—	—
HER2 genotype‡					
Dominant mode of inheritance					
Ile/Ile	432 (57.9)	—	—	1.00 (referent)	1.00 (referent)
Ile/Val and Val/Val	314 (42.1)	—	—	0.70 (0.30 to 1.85)	1.51 (0.83 to 2.49)
Recessive mode of inheritance					
Ile/Ile and Ile/Val	707 (94.8)	—	—	1.00 (referent)	1.00 (referent)
Val/Val	39 (5.2)	—	—	1.37 (0.00 to 3.98)	2.54 (0.40 to 3.63)
Total	746 (100.0)	189 (100.0)	2231 (100.0)		

*Originally, 748 case probands provided data on 2436 first-degree female relatives (190 with and 2246 without breast cancer). After exclusion of two probands with missing HER2 genotype and their 10 relatives plus six relatives with unknown exit age, we analyzed data from 746 case probands and 2420 relatives (189 with and 2231 without breast cancer). Relatives were followed from birth to breast cancer diagnosis or death or were censored at the date of interview of the proband, whichever came first. The HER2 genotype of the relatives is inferred from the genotyped case patients with breast cancer by use of the kin–cohort design. CI = confidence interval. Val = valine; Ile = isoleucine.

†Case probands.

‡Frequency of valine (Val) allele = 24%; χ^2 test for Hardy–Weinberg equilibrium in case probands, $P = .86$.

years and 2.54 (95% CI = 0.40 to 3.63) up to age 70 years (Table 1). The estimated absolute risk at age 70 years among women with the Val/Val genotype was 0.25 (95% CI = 0.04 to 0.34).

This kin–cohort study is a useful supplement to the case–control design because case probands are prevalent and, therefore, survival might affect the case–control analysis but not the kin–cohort analysis. In addition, relatives of radiologic technologists do not have an elevated background risk of breast cancer from occupational radiation exposure. Our kin–cohort analysis used relatives of case patients with breast cancer, so that absolute risk estimates would be too high if there are other sources of familial aggregation. Furthermore, RR estimates reflecting the effect of the HER2 genotype in subjects with a family history of breast cancer may not be equal to RRs in the general population if HER2 interacts with other familial risk factors.

Although we did not find a statistically significant association in our relatively small study, given the prior associations between the HER2 Val allele and the risk of breast cancer *(1,2,7),* our observation of an RR of 2.5 by age 70 years suggests that the association might be real. We did not, however, confirm that the effect is especially pronounced at younger ages *(1,2).* Additional information on the functional relevance of the HER2 Val allele would substantially improve the final interpretation of whether it is a risk allele for breast cancer.

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NOTES

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